New Jersey Commission On Cancer Research

Snapshot of Research Projects From

5TH ANNUAL CANCER RESEARCH SYMPOSIUM

(VIRTUAL)

November 10, 2021

Background:

Presentations at the NJCCR symposium were given virtually by Predoctoral and Postdoctoral research scientists. These research presentations stem from grant awards by the New Jersey Commission on Cancer Research. Grant awards are given to attract and retain talented scientists (fellowships) who wish to pursue a career in cancer research in New Jersey. The goal of the Fellowship program is to provide funding for fundamentally sound research proposals that award recipients and their laboratories, who have identified new research and innovations to fight the war on cancer.

The first four pages consist of a snapshot of the cancer research presentations and includes the following:

Title: Ligand-directed α-galactosyltransferase gene therapy using hybrid AAV phage vector for antitumor immune response.

Summary: Cancer immunotherapy is a treatment that involves a patient's immune system to fight cancer. The immune system protects the body from infections and other diseases including cancer by attacking any new substance that is not normally found in the body. When normal cells become cancerous, they are altered and can produce certain proteins that the immune system does not recognize. This research project focuses on modifying a virus to infect only cancer cells that improve immune recognition and elimination of cancer cells.

Title: A clickable, free radical-mediated drug delivery system for cancer treatment.

Summary: Free radicals contribute to the development and spread of ovarian cancer, and elevated levels of free radicals are present in nearly all types of cancer. We have hypothesized that these radicals can induce a healthy therapeutic molecule. If successful, this approach will improve cancer treatment by localizing and sustaining the presence of healthy molecules at the tumor site.

Title: The effects of intratumoral heterogeneity in triple-negative breast cancer on metastasis and chemotherapeutic response.

Summary: One in eight women will be affected by breast cancer at some point in their lives. Approximately 15-20% of these women will be diagnosed with triple-negative breast cancer (TNBC), which is characterized by the absence of three specific receptors in the cancer cells. TNBC is notoriously difficult to treat, and patients often have a lower overall survival rate compared to patients with other types of breast cancer. This study examines several models that could potentially be used to test chemotherapies from patient samples before they are delivered to patients thus leading to improved outcomes.

Title: Investigating the impact of (Lung Cancer) autophagy deficiency on the tumor microenvironment.

Summary: Lung cancer is a deadly disease and one of the leading causes of death worldwide, and thus needs new therapeutic approaches. This research project examines the mechanisms that lead to impaired tumor growth.

Title: The Role of Sliding in Cohesin Accumulation and Function on Chromosomes.

Summary: This research examines the mutations of some forms allowing a better understanding of the biology of chromosomal sites.

Title: Systematic Detection of Oncogenic TAD Disruption Across Cancer Types.

Summary: Cancer is a disease where our cells acquire damage that allows them to grow uncontrollably. The specific changes observed in the DNA of tumor cells differ across individuals, and the goal of cancer genomics is to uncover cancer-driving changes in tumors and then use

this knowledge to develop individualized cancer treatment plans.

Title: Neoadjuvant chemotherapy and targeted therapies in ovarian cancer: Racial disparities in use and survival outcomes.

Summary: Ovarian cancer is the 5th most common cause of cancer deaths in women and the most common cause of death in gynecologic cancers in the United States and women in New Jersey. More than 70% of the patients are diagnosed at the advanced stage with a dismal 5-year survival rate of 40%. Survival is the worst for African American women, who experience a 41% higher mortality rate compared to non-Hispanic White women after accounting for age and stage of the disease. Neoadjuvant chemotherapy has become an accepted alternative first-line treatment for patients with extensive tumor burden or poor performance. Due to the low survival associated with current therapies, little attention has been given to the differences in the use of NACT and targeted therapies and how these potential differences may explain persistent racial disparities in survival after an ovarian cancer diagnosis. This study will look at 4,385 patients diagnosed with ovarian cancer and determine how receiving NACT and targeted therapies contribute to existing racial/ethnic ovarian cancer survival disparities.

Title: ACLY as a novel therapeutic target in T-cell leukemia

Summary: T-lineage acute lymphoblastic leukemia (T-ALL) is an aggressive cancer of the blood that is driven by a gene called NOTCH1. Despite recent progress in clinical outcomes in this disease, 25% of children and over 50% of adult T-ALL cases show primary resistant leukemia or respond only transiently to chemotherapy, and ultimately succumb to their disease, highlighting the need to discover improved agents. Our preliminary data point to the fact that ACLY (an enzyme involved in the control of both metabolism and gene expression) could play a key role but was previously unrecognized. The main objective of this study is to address the role of ACLY in T-All. The results could directly translate into improved treatments for all patients with this disease.

Title: Identifying the role of CPT1A and fatty acid oxidation in endocrine therapy resistance in ER+ Breast Cancer

Summary: Breast cancer is the most commonly diagnosed and second leading cause of cancer-related deaths in women. Hormone receptors positive (HR+) breast tumors account for approximately 70% of the nearly 270,000 diagnosed breast cancer cases each year. Since these tumors are dependent on estrogen signaling for tumor growth, most patients are successfully treated with endocrine-based therapies that block this signaling. Unfortunately, between 30% and 50% of these tumors are resistant or will develop resistance to these treatments. This results in tumor recurrence and disease progression, including cancer spreading to other organs in the body and ultimately leading to death. While several recent advances have led to new treatments for these patients, understanding the mechanisms that play role in HR+ remains an unmet need. This study will begin to identify the genetic alterations and the role of a gene (CPT1A) as a therapeutic option for the treatment of breast tumors.

Title: Uncovering the shared T cell specificities in lung cancer patients for the development of novel T cell receptor-engineered T cell therapy

Summary: T cells are an integral part of the immune response against cancer. This study attempts to identify the T cell clones with functional avidities against shared tumor antigens that will be less likely to cause severe toxicities.

Title: Elucidating the role and mechanism of the ketogenic diet in KRAS-mutant lung tumorigenesis

Summary: Lung cancer remains one of the leading causes of cancer-related death, with non-small cell lung cancer (NSCLC) representing almost 85% of all cases. KRAS is the most common oncogenic driver in NSCLC, confers a poor prognosis, resistance to therapy, and is undruggable. The purpose of this scientific research is to gain a better understanding of how the genetic makeup determines the response of different subtypes of KRAS-driven lung tumors to a

ketogenic diet. A ketogenic diet may prove to be invaluable as an adjuvant for cancer therapy.

Title: The role of glutaminolysis in T-ALL

Summary: T-lineage acute lymphoblastic leukemia (T-ALL) is an aggressive cancer. Despite recent progress in clinical outcomes in this disease, 25% of children and over 50% of adult T-ALL cases show primary resistant leukemia or respond only transiently to chemotherapy, and ultimately succumb to their disease. Glutaminolysis is a metabolic route that we have found is critical for the proliferation of T-ALL cells. The main objective of this study is to understand the mechanism that cancer cells use to escape this metabolic route.

Title: The role of Metadherin (MTDH) in suppressing the immune response to metastatic breast cancer

Summary: Breast cancer has been the leading diagnosed cancer type in women of the U.S. in 2018, with an estimated 266,120 new cases and accounts for 30% of all new cancer diagnoses in women. Tumor metastasis is the major reason that has resulted in a high rate of breast cancer mortality. Tumor cells can escape the immune surveillance and spread to other distant organs, including the lung, liver, and bone. However, the exact cellular and molecular mechanism of tumor metastasis remain elusive. A better understanding of the mechanism of how breast cancer cells interact with immune cells in the tumor could provide a better strategy for patients with metastatic breast cancer.

Below is a summary of the full abstracts and includes the following:

Author: Svetlana Bagdasarov, Rutgers

Title: Ligand-directed α-galactosyltransferase gene therapy using hybrid AAV phage vector for antitumor immune response

Lay Abstract: Cancer immunotherapy is a treatment that involves a patient's immune system to fight cancer. The immune system protects the body from infections and other diseases including cancer by attacking any new substance that is not normally found in the body. When normal cells become cancerous, they are altered and can produce certain proteins that the immune system does not recognize. Antibody binding or targeting by special immune cells raises an alarm to destroy these foreign cells. In many people who develop cancer, the immune system does not work because some types of cancer are not different enough from normal cells to be recognized as foreign. To overcome this, our strategy for this research project is to modify a prokaryotic virus to infect only cancer cells to improve immune recognition and elimination of cancer cells. Prokaryotic viruses infect and replicate within bacteria alone and lack the intrinsic ability to infect mammalian cells. These viruses have a long history of safe delivery to humans to treat bacterial infections. In addition, they can be modified to target mammalian cells that have specific receptors, a property our group will use to deliver an immune-stimulating gene to tumors. This gene, called a-1,3-galactosyltransferase (Ggta1), makes a protein that transfers a Gal carbohydrate to the surface of cells. Ggta1 is found in large amounts in most mammals, however, is absent in humans. As a result, humans lack Gal carbohydrate, and antibodies to Gal are the most abundant natural antibodies in human blood. Pig organs transplanted in humans are rapidly rejected because anti-Gal antibodies interact with the Gal carbohydrate on pig tissue and destroy the transplanted organ. Delivery of the Ggta1 gene specifically to cancer cells will enable them to express this carbohydrate that will bind to anti-Gal antibodies to attack the tumor by the same mechanism. The development of this new virus-based targeted gene therapy may enhance the immune response to identify and attack tumor cells and directly benefit cancer patients. In this study, the described treatment approach will be probed on mouse models of two types of cancer, pancreatic neuroendocrine tumors, and melanoma. However, this targeted treatment methodology is quite versatile with potential application to a wide variety of cancers.

Author: Emily DiMartini, Rutgers

Title: A clickable, free radical-mediated drug delivery system for cancer treatment

Lay Abstract: Free radicals contribute to the development and spread of ovarian cancer, and elevated levels of free radicals are present in nearly all types of cancer. We have hypothesized that these radicals can also induce crosslinking of a polymer carrying a therapeutic molecule. In polymer chemistry, the high reactivity of free radicals is widely used to initiate crosslinking and control polymerization. For example, polyethylene glycol (PEG) is a commonly used polymer for biomedical applications, and acylating the PEG allows it to react with free radicals and crosslink with other acrylate PEGs. The crosslinking reaction makes the PEG substantially larger and less mobile. Since the tumor has the largest concentration of free radicals relative to healthy tissues, this crosslinking reaction would immobilize the polymer and attach therapeutic molecules at the cancer site. We have previously demonstrated that relevant free radicals can polymerize and crosslink acrylate PEG to immobilize a network – and any molecules that it carries – within a tissue mimic. We now propose to build on these promising results and expand our approach into a two-step "catch-and-release" system. Instead of delivering the drug at the same time as the immobilization polymers, we will deliver one component of a click chemistry pair with the acrylate PEGs. Click chemistry reactions are highly efficient and specific, and the individual click groups do not interfere with neighboring biological reactions. Elevated free radicals at the tumor site will initiate crosslinking,

immobilizing polymers, and one piece of the click chemistry pair. The therapy can be delivered at a later time conjugated to a separate, orthogonal click group, and the payload is trapped at the tumor site via the click chemistry reaction. A two-phase approach allows flexibility over the timing of delivery and dosage of the therapeutic. The proposed system also includes degradable linkers within the polymer backbones that are split by enzymes upregulated in the tumor. These linkers allow the payload to be released locally within the tumor over time so that the therapeutic can enter cells, instead of having it permanently immobilized where it can act only as an extracellular ligand. We will develop the system in vitro and with ovarian cancer 3D cell models, and then demonstrate the "catch-and-release" of a fluorescent molecule in vivo. If successful, our approach will improve cancer treatment by localizing and sustaining the presence of therapeutic molecules at the tumor site.

Author: Molly Brennan, Princeton University

Title: The effects of intratumoral heterogeneity in triple-negative breast cancer on metastasis and chemotherapeutic response

Lay Abstract: One in eight women will be affected by breast cancer at some point in their lives. Approximately 15-20% of these women will be diagnosed with triple-negative breast cancer (TNBC), which is characterized by the absence of three specific receptors in the cancer cells. TNBC is notoriously difficult to treat, and TNBC patients often have a lower overall survival rate compared to patients with other types of breast cancer. The poor prognosis of TNBC patients may be due to the composition of the tumor itself. As the tumor grows, individual cells acquire modifications to their genome, epigenome, transcriptome, and proteins. Cells in the tumor can also undergo epithelial-mesenchymal transition (EMT). Epithelial cells adhere tightly to each other while mesenchymal cells are more migratory and form loose attachments to their neighbors. After some time, the tumor can be composed of several clonal populations that may have different phenotypes and behaviors. This is known as intratumoral heterogeneity. As these clonal populations may react differently to chemotherapy, it can be difficult to determine what treatments may kill all of the cells within a tumor. These clonal populations may also have different metastatic potentials. Cancer-related deaths are mainly caused by metastasis. Metastasis occurs when cancer cells invade the healthy tissue around the initial tumor, enter the blood and lymphatic vessels, and travel throughout the body. If the cancer cells leave these vessels in distant organs, they can proliferate in those organs and form metastases. In a heterogeneous tumor, some clonal populations may be more likely to metastasize than others or may increase the metastatic potential of other clonal populations. Intratumoral heterogeneity is hypothesized to contribute to the aggressiveness and poor prognosis of TNBC but has been challenging to study. The overall goal of this proposal is to use novel engineering strategies to evaluate the effects of intratumoral heterogeneity on metastasis and susceptibility to chemotherapeutics. The first two aims evaluate the metastatic potential and responsiveness to treatment of homogeneous and heterogeneous populations of a murine TNBC cell line, from which my lab has derived two epithelial and two mesenchymal clonal populations. Aim 1 will examine the behaviors of homogeneous epithelial and mesenchymal populations and heterogeneous populations in an engineered tumor model. Within the model, we can study proliferation and local invasion and escape to learn more about how these populations behave in the initial steps of the metastatic cascade. Aim 2 will use an in vivo chick chorioallantois membrane assay to assess the ability of the different populations to form tumors, intravasate into the vasculature, and form metastases. In both aims, we will also assess the responses of these populations to new chemotherapy treatment strategies. The third aim will use the two models to examine the metastasis and chemotherapeutic responses of cells derived from human tumors. Through a collaboration with Rutgers University, residual tumor samples from TNBC patients currently in a clinical trial will be placed within these models. Using the genomic profiling performed by

the researchers conducting the clinical trial, the heterogeneity of these tumors will be assessed. Furthermore, while physicians can often only observe the tumor size and locations of metastases in patients, after placing the patient samples in these models we will observe the behaviors of cancer cells at specific steps in the metastatic cascade. Additionally, we will observe responses to chemotherapy and compare the responses in our models to the responses of the patients in the clinical trial. In the future, these models could potentially be used to test chemotherapies on patient samples before they are delivered to patients and improve precision medicine.

Author: Maria Ibrahim, Rutgers University

Title: Investigating the impact of autophagy deficiency on the tumor microenvironment

Lay Abstract: Lung cancer is a deadly disease and one of the leading causes of death worldwide, and thus needs new therapeutic approaches [1]. Autophagy is the mechanism by which cells recycle proteins and organelles to maintain cellular homeostasis during stress and starvation [4]. Under normal conditions, autophagy functions at a low basal level to remove damaged cellular components, thus preventing the gradual accumulation of toxic, intracellular waste material [4]. Cancer cells rely on autophagy -- in many cases, they are more autophagy-dependent than normal cells and tissues. This is due to the inherent deficiencies in the surrounding microenvironment caused by increased metabolic and biosynthetic demands imposed by deregulated cell proliferation. A major limitation is that most cancer models have addressed the role of autophagy only in tumors without drawing a direct comparison to autophagy deficiency in normal tissues. We propose to use a GEMM of systemic ablation of essential autophagy gene 7 (Atg7) to explore the underlying metabolic phenotype associated with autophagy deficiency and the tumor microenvironment [3]. Acute, whole-body deletion of Atg7 in adult mice causes a systemic metabolic defect manifested by gradual loss of white adipose tissue, liver glycogen, and muscle mass [3]. Hence, we propose that the overall alterations in energy balance, consumption, and macro-fuel combustion contribute to the metabolic phenotype underlying autophagy deficiency. Autophagy promotes tumor growth through both metabolic and immune mechanisms by regulating immune cell homeostasis and function and suppressing inflammation [15]. Previous data from the lab demonstrated that loss of autophagy promotes an antitumor T cell response in high tumor mutation burden tumors [12]. Additionally, serum cytokine and chemokine analysis demonstrated an increase in interferon-induced cytokine signaling upon loss of autophagy. We propose loss of autophagy causes systemic alterations in immune infiltration leading to metabolic changes within the tumor microenvironment. Lastly, the mTOR pathway integrates a diverse set of environmental cues, such as growth factor signals and amino acids levels, in cell growth. Arginine is known to activate mTOR1 and systemic loss of Atg7 results in degradation of circulating arginine essential for tumor growth [11]. We will elucidate whether the decrease in mTOR activity is causing arginine loss in autophagy-deficient mice leading to impaired tumor growth. In conclusion, this research plan will investigate the metabolic phenotype in autophagy-deficient mice and tumor microenvironment.

Author: Paul Kraycer, Rutgers University

Title: The Role of Sliding in Cohesin Accumulation and Function on Chromosomes

Lay Abstract: Mutations in the cohesin complex or its regulators are linked with some forms of cancer, such as Urothelial carcinoma, Ewing Sarcoma, and myeloid neoplasms. How dysfunctional cohesin leads to cancer is not fully understood. The fact that cohesin mediates nearly every aspect of chromosome biology leaves open a wealth of possible mechanisms. To appreciate cohesin's role in cancer, it is necessary to first understand its normal roles in chromosome biology. Cohesin loads at specific locations and then redistributes to other key sites of chromosomes where the complex is thought to act. How this occurs is not completely understood. Cohesin slides along purified DNA but whether sliding occurs in living cells has not been established. I hypothesize that redistribution of cohesin by sliding is a universal process that moves the complex to critical sites of action and away from harmful locations on

chromosomes. Thus, the central goals of this proposal are two-fold: 1) to understand how cohesin redistributes on yeast chromosomes; 2) to determine how cohesin contributes to the biology of chromosomal sites where the complex accumulates.

Author: Judy T. Du, Princeton University

Title: Systematic Detection of Oncogenic TAD Disruption Across Cancer Types

Lay Abstract: Cancer is a disease where our cells acquire damage that allows them to grow uncontrollably. The specific changes observed in the DNA of tumor cells differ across individuals, and the goal of cancer genomics is to uncover cancer-driving changes in tumors and then use this knowledge to develop individualized cancer treatment plans. Towards this end, there have been extensive experimental genomics efforts to characterize tumor cells across large numbers of patients with different cancer types, to discover what changes occur, which changes have effects, and why they contribute to cancer. The resulting data allow one to look at a specific patient's genome to determine which genes in cancer cells are turned on ("expressed") or off, and which portions of genomic DNA are damaged by mutation, deletion, or chemically modification. However, complex analytical methods are necessary to link which of the many observed alterations are relevant for cancer. Broadly speaking, I propose to develop computational methods and accompanying software to analyze cancer genomics data to uncover the genomic mechanisms underlying cancer initiation and progression.

More specifically, I will focus on identifying cancer-relevant genes that are improperly expressed due to changes in the 3D organization of DNA. Recently, it has been discovered that DNA is organized into 3D physical compartments that encompass genes and the regions of the genome that regulate their expression. Notably, the disruption of these compartments has been shown in experiments to alter gene expression and promote enhanced cellular growth within glioblastomas, ovarian cancer, T-cell acute lymphoblastic leukemia, and acute myeloid leukemia. However, there has not been a systematic, genome-wide study to identify whether disruption of the 3D compartments within a diverse set of cell types contributes to cancer progression. Understanding the mechanisms by which carcinogenic DNA dysregulates the normal expression of genes is important for understanding the molecular basis of cancer and will be an important step in leading the way for future targeted therapies.

I am proposing to build software to analyze cancer genomics datasets to identify signatures of regulatory compartment disruption - whether due to mutation, chemical modification, or larger rearrangements of DNA. Next, I will build statistical models that test whether these candidate disruptions of chromosomal compartments have a functional effect on gene expression. My novel approach will enable the systematic study of the effects of compartment disruption on gene dysregulation in cancer and will vastly advance our understanding of functional alterations in cancer genomes. My set of software tools will be made publicly available and streamlined for use by both biologists and computational scientists.

Post-doctoral Presentations

Author: Saber Amin, Rutgers University

Title: Neoadjuvant chemotherapy and targeted therapies in ovarian cancer: Racial disparities in use and survival outcomes

Lay Abstract: Ovarian cancer is the 5th most common cause of cancer deaths in women and the most common cause of death in gynecologic malignancies in the United States and women in New Jersey. More than 70% of the patients are diagnosed at the advanced stage with a dismal 5-year survival rate of 40%. Survival is worst for African American (AA) women, who experience 41% higher mortality compared to non-Hispanic White (NHW) women after accounting for age and stage. The causes for these disparities are likely to be multi-factorial; some of the factors implicated include stage and grade at diagnosis, adherence to treatment guidelines, and access to care. Primary cytoreductive surgery followed by platinum-based adjuvant chemotherapy is the standard treatment option. However, not all patients are candidates for upfront surgery followed by chemotherapy. Neoadjuvant chemotherapy (NACT) has become an accepted alternative first-line treatment for patients with extensive tumor

burden or poor performance. Due to the low survival associated with current therapies, novel treatment strategies such as targeted therapies have shown promising results. However, little attention has been given to differences in the use of NACT and targeted therapies and how these potential differences may explain persistent racial disparities in survival after an ovarian cancer diagnosis. We propose to evaluate these associations leveraging the KP ROCS (Kaiser Permanente-Research on Ovarian Cancer Survival) Study, a large cohort study of ovarian cancer survivors among Kaiser Permanente Northern California (KPNC) members. Our specific aims are to 1) characterize patient and clinical factors associated with the use of neoadjuvant chemotherapy and targeted therapy, including differences by race, after controlling for other relevant factors; 2) evaluate differences in the impact of neoadjuvant and targeted therapy on ovarian cancer survival outcomes (ovarian cancer-specific survival and overall survival) by race, and 3) investigate how receiving neoadjuvant chemotherapy and targeted therapy contribute to existing racial/ethnic ovarian cancer survival disparities. The study will include 4,385 patients (AA:266, NHW:3126, Hispanic:290, Asian:610, and Other=93) diagnosed with ovarian cancer between 2000 and 2018 at KPNC. We will perform multivariable logistic regression analysis and report the odds ratio as a measure of association for factors associated with receiving neoadjuvant chemotherapy and targeted therapy with race as one of the predictors. For aims 2 and 3, multivariable Cox Proportional Hazards regression analysis will be used to assess the association of the various factors mentioned above, including NACT and targeted therapies with ovarian cancer survival. The current study will be the first and most comprehensive analysis to examine racial disparities in receiving NACT and targeted therapy and investigate the contribution of any potential treatment disparities to disparities in survival. Findings from the study will have a direct translational clinical impact at KPNC, New Jersey, and nationwide in managing diverse ovarian cancer patients and contributing to reducing cancer health disparities. This award will also be crucial as a first step to gathering preliminary data to support an NIH K99/R00 application submission and to start my research program in cancer health outcomes, with a focus on disparities research.

Author: Patricia Renck Nunes, Rutgers University

Title: ACLY as a novel therapeutic target in T-cell leukemia

Lay Abstract: T-lineage acute lymphoblastic leukemia (T-ALL) is an aggressive hematologic malignancy driven by a gene called NOTCH1. Despite recent progress in clinical outcomes in this disease, 25% of children and over 50% of adult T-ALL cases show primary resistant leukemia or respond only transiently to chemotherapy, and ultimately succumb to their disease, highlighting the need to discover novel and improved therapeutic targets. Our preliminary data point to the fact that ACLY (an enzyme involved in the control of both metabolism and gene expression) could play a key but previously unrecognized role in this disease. Thus, the main objective of this study is to address the role of ACLY in T-ALL in vivo using refined genetic mouse models and experimental therapeutic assays. The results from this project could directly translate into improved treatments for T-ALL patients in the short term.

Author: Shaimaa Hussein, Rutgers

Title: Identifying the role of CPT1A and fatty acid oxidation in endocrine therapy resistance in ER+ Breast Cancer

Lay Abstract: Breast cancer is the most commonly diagnosed and second leading cause of cancer-related deaths in women in the United States. Hormone receptors positive (HR+) breast tumors account for approximately 70% of the nearly 270,000 diagnosed breast cancer cases each year. Since these tumors are dependent on estrogen signaling for tumor growth, most patients are successfully treated with endocrine-based therapies (ET) that block this signaling. Unfortunately, between 30% and 50% of HR+ tumors are resistant or will develop resistance to these treatments. This results in tumor recurrence and disease progression, including metastases to other organs in the body, and ultimately leads to death. While several recent advances have led to new treatments for these patients, understanding the mechanisms that promote estrogen-independent HR+ tumor growth and identifying new therapeutic options for these patients remains an essential unmet need. To begin to identify these genetic alterations, we analyzed data from more than 3,000 breast tumors. Our analyses identified overexpression

of the gene carnitine palmitoyltransferase 1 A (CPT1A) in aggressive and ET-resistant HR+ breast tumors. CPT1A regulates Fatty Acid ß Oxidation (FAO) which is a metabolic process by which cells generate energy and has been shown to play an important role in tumor development and progression in other forms of cancer. Importantly, several drugs that inhibit CPT1A or FAO have been approved by the FDA or internationally for cardiac patients. Consistent with the potential role of CPT1A and FAO in HR+ tumor growth, we determined that shRNA-mediated silencing of CPT1A or pharmacological inhibition of FAO results in decreased cell growth and increased cell death. Moreover, we determined that cell lines or tumor models that develop resistance show increased CPT1A expression. Based on our preliminary data, we hypothesize that CPT1A and fatty acid oxidation (FAO) contribute to the development of endocrine therapy resistance in HR+ breast cancer. We further propose that CPT1A/FAO represents a novel therapeutic target to enhance ET response and prevent the emergence of acquired resistance. The goals of the proposed research are (1) to determine the role of CPT1A and FAO in the development of acquired endocrine therapy resistance in HR+ breast cancer and (2) to examine the therapeutic potential of targeting FAO or CPT1A to enhance response to endocrine therapy and prevent the emergence of ET resistance. Should our hypothesis be correct, we anticipate that the proposed studies will begin to delineate the role of CPT1A and FAO in endocrine therapy resistance and provide preclinical data to support the potential impact of FAO inhibitors as a therapeutic option for the treatment of HR+ breast tumors.

Author: Sai Zhang, Rutgers University

Title: Uncovering the shared T cell specificities in lung cancer patients for the development of novel T cell receptor-engineered T cell therapy

Lay Abstract: T cells are an integral part of the immune surveillance against cancer. Chimeric antigen receptor (CAR)-T therapy showed remarkable efficacy in the treatment of certain blood cancers, but not epithelial or solid cancers. Conversely, genetically engineered T cells carrying T cell receptors (TCRs) that target specific tumor-associated antigens, or TCR-T therapy, have demonstrated more success in treating patients with solid cancers, although severe toxicities caused by the infused T cells were documented. For the development of successful TCR-T therapy, it is incredibly challenging to identify novel TCR clones with clinical significance due to the exceptionally high diversity of TCR clonotypes. Thus, a novel strategy that allows a systematic discovery of TCR candidates with 1) a superior functional avidity to target cancer cells and 2) tolerance to the otherwise healthy tissues will transform the current method of developing efficacious adoptive TCR-T cell therapy. Lung cancer is the leading cause of cancer-related deaths in the United States, with non-small cell lung cancer (NSCLC) being the most common form of this cancer type. NSCLC patients with advanced disease have an extremely low 5-year survival rate of around 6%. Immune checkpoint blockade (ICB) is a therapeutic regimen that blocks the "off signal" sent to T cells, leading to enhanced anti-tumor activity. However, only a small subset of patients with advanced or metastatic disease showed durable benefits from the treatment. Numerous studies showed that T cells targeting neoantigens, i.e., proteins derived from mutated genes, are an important element in the clinical responses to the ICB treatment. However, cancers bearing a high mutation burden, which usually means a higher level of neoantigens being presented, do not always lead to a durable response to the ICB treatment. In contrast to T cells targeting neoantigens, little is known about the role of T cells targeting non-mutated, shared antigens in the setting of ICB treatment in cancer. In adoptive T cell therapy, T cells targeting non-mutated antigens, including germline cancer antigens or viral antigens, could play essential roles in tumor regression. Thus, identifying these TCR clones that are enriched in ICB responders would facilitate the development of new TCR-T cell therapy with better efficacies. In the proposed study, we hypothesize that 1) by uncovering the TCR specificity groups that are enriched in ICB responders, we can identify T cell clones with superior functional avidities against shared tumor antigens, and 2) these naturally occurring TCR clones will be less likely to cause severe toxicities when used as TCR-T cell therapy due to central tolerance, as high-avidity self-reactive T cells are usually eliminated during T cell development.

Author: Fawzi Alogaili, Rutgers University

Title: Elucidating the role and mechanism of the ketogenic diet in KRAS-mutant lung

tumorigenesis

Lay Abstract: Lung cancer remains one of the leading causes of cancer-related death, with non-small cell lung cancer (NSCLC) representing almost 85% of all cases. KRAS is the most common oncogenic driver in NSCLC, confers a poor prognosis, resistance to therapy, and is undruggable so far. Co-mutations of LKB1 or TP53 define different subgroups of KRAS-mutant NSCLC with distinct biology, therapeutic vulnerabilities, immune profiles, and responses to the treatments. Therefore, personized therapy for different subgroups of KRAS-mutant NSCLC is necessary. Cancer cells undergo oncogene-directed metabolic reprogramming to support cell growth and survival. The complex metabolic alterations not only affect the metabolic network within cancer cells but can also influence metabolism at the organismal level and host. Metabolic interventions such as the ketogenic diet, which is high in fat and low in carbohydrates as well as protein, modulate host metabolism by forcing cells to rely on lipid oxidation and mitochondrial respiration rather than glycolysis for energy metabolism. Since cancer is a metabolic disease, we assessed the metabolic alterations in both tumor and host using KRAS-driven genetically engineered mouse models (GEMMs) for KrasG12D/+; Lkb1-/- (KL) or Kras G12D/+; p53-/- (KP) NSCLC via in vivo isotope tracing and systematic analyses of lipogenesis flux. We found that hepatic de novo lipogenesis was reduced among different subtypes of Kras-driven lung cancer. Interestingly, the Ketogenic diet alters host metabolism, including lipid metabolism; but the role of the ketogenic diet in Kras-driven NSCLC tumorigenesis and cancer treatment has not been well explored. We, therefore, treated the mice with a ketogenic diet when KL or KP lung tumors were induced in mice. Unexpectedly, we observed that the ketogenic diet promoted KL lung tumorigenesis, but inhibited KP lung tumor growth. However, the ketogenic diet alone did not affect the established KL and KP lung tumor growth. Our study indicates a unique role of the ketogenic diet in the initiation of KL and KP lung tumors. Thus, understanding how the genetic makeup determines the response of different subtypes of KRAS-driven lung tumors to a ketogenic diet is critical to providing strategies for using a ketogenic diet as an adjuvant for cancer therapy. Here, we will determine the underlying mechanism by which the ketogenic diet modulates tumor and host metabolism to cause distinct responses in the development of KL and KP lung tumors. We will also explore if the ketogenic diet can act as an adjuvant in the treatment of KRAS-driven lung cancer.

Author: Maria Victoria da Silva Diz, Rutgers

Title: The role of glutaminolysis in T-ALL

Lay Abstract: T-lineage acute lymphoblastic leukemia (T-ALL) is an aggressive hematologic malignancy driven by NOTCH. Despite recent progress in clinical outcomes in this disease, 25% of children and over 50% of adult T-ALL cases show primary resistant leukemia or respond only transiently to chemotherapy, and ultimately succumb to their disease. Glutaminolysis is a metabolic route that we have found is critical for the proliferation of T-ALL cells. Therefore, inhibiting glutaminolysis with drugs or using refined genetic experiments that completely abrogate glutaminolysis, translates into significant anti-leukemic effects. However, albeit with delayed kinetics, T-ALL cells that cannot use glutaminolysis eventually progress, which suggests that human T-ALL patients treated with glutaminase inhibitors would invariably relapse. Thus, the main objective of this study is to understand the mechanism that cancer cells use to escape the block in glutaminolysis. In addition, we want to address the role of glutaminase in cancer stem cell biology. These findings can help us to develop new targeted therapies that might overcome this resistance, but also for other cancer types where glutaminolysis plays a major role.

Author: Yong Tang, Princeton University

Title: The role of Metadherin (MTDH) in suppressing the immune response to metastatic breast cancer

Lay Abstract: Breast cancer has been the leading diagnosed cancer type in women of the United States in 2018, with an estimated 266,120 new cases and accounts for 30% of all new cancer diagnoses in women. Tumor metastasis is the major reason that resulted in a high rate of breast cancer-related mortality. Tumor cells can escape the immune surveillance and spread

to other distant organs, including the lung, liver, and bone. However, the exact cellular and molecular mechanism of tumor metastasis remain elusive. A better understanding of the mechanism of how breast cancer cells interact with immune cells in the tumor microenvironment and how breast cancer cells suppress the immune response to metastasis could potentially provide a better therapeutic strategy for those patients with metastatic breast cancer.

Our previous studies identified Metadherin (MTDH) as a functional gene that is associated with poor prognosis breast cancer patients. MTDH can regulate oncogene-induced expansion and activities of tumor-initiating cells to promote mammary tumorigenesis. Our recent findings indicated that tumor-intrinsic expression of MTDH may promote mammary tumorigenesis and lung metastasis by suppressing the immune response. In this study, I will address the specific overarching challenge of identifying the cellular and molecular mechanism that MTDH facilitates the escape of tumor cells from immune surveillance to metastasis. First, I will determine the targeted immune cell population by MTDH-expressed tumor cells. By combining genetics mouse models and a variety of cellular or molecular methods, I will comprehensively elucidate the underlying mechanisms of interaction between MTDH-expressed tumor cells and their targeted immune cells. Additionally, I will analyze the clinical database or breast tumor samples to establish a correlation of MTDH expression and tumor infiltrated immune cells. Finally, I will test the treatment strategies in mouse models by combining MTDH inhibition with immunotherapy.

The research results from this project may have a broad impact on the field of breast cancer metastasis and tumor immunotherapy. MTDH has been well established as a metastatic protein, and my proposed study will broaden its metastatic function by facilitating the escape of tumor cells from immune surveillance. Combining MTDH inhibition and immunotherapy may be a new treatment to prevent breast cancer metastasis. Since MTDH is overexpressed in more than 40% of primary breast tumors, our new findings may be helpful to relieve the suffering of those breast cancer patients.

The Keynote Address below was given by Dr. Shawna Hudson, Ph.D. Professor, Henry Rutgers

Professor, Henry Rutgers Chair and Research Division Chief, Family Medicine and Community Health
Rutgers Robert Wood Johnson Medical School

Title: Cancer Survivorship Healthcare Delivery: Challenges and Opportunities for Implementation Science and Intervention Research

Key Highlights:

- **Implementation Research**
  - The scientific study of the use of strategies to adopt and integrate evidence-based health interventions into clinical and community settings to improve individual outcomes and benefit population health.
- **Primary Care: A Central Issue in Survivorship**
  - "The involvement of primary care providers is now regarded as a central issue in survivorship care given the growing demand for acute cancer treatment services that is taxing existing resources, the rising prevalence of comorbid conditions among cancer survivors, and the increased emphasis on value in U.S. medical care reimbursement policies…there is much preliminary work that needs to be done"
- **Care of Long-term Cancer Survivors**
  - 1/3 of long-term cancer survivors continue to seek care from cancer and cancer-related specialists after 5 years of survival
  - 75% of survivors receive care from PCPs
  - Patients with the localized disease were significantly more likely to receive care from PCPs than cancer or cancer-related specialists.
- **Patients Want "the Best" Specialty Care**
  - Prepare patients for self-management of follow-up care
  - Patient Relationship with Primary Care
  - Extended Care Education for Long-term Survivors in Primary Care (EXCELS)
  - Self-management intervention for early-stage cancer patients in primary care
- **Limited Financial Incentives for Survivorship Care in Primary Care**
  - "The productivity pay structure…rewards doctors for high-volume care, not necessarily high-quality care,"
  - **Cancer Survivors Not a Distinct Population in Primary Care**
  - "I certainly don't think of [these patients] as cancer survivors. I think of them as people living with a history that's not terribly unlike the history of diabetes or any other chronic disease."
- **Current Information Systems are Insufficient to Support Survivorship Care**
  - EHR problem lists are not "user-friendly," which requires searching multiple screens to find any mention of cancer
- **Clinicians Still Receive Limited Information or Follow-Up Guidance on Patients' Cancer Care**
  - Some practices received cancer-related information about their patients or care summaries, but it was either inadequate or not actionable

- **Adapting and implementing evidence-based cancer follow-up in primary care**
    - Engage diverse primary care stakeholders in identifying actionable, practice-based activities for the provision of long-term breast cancer survivorship care in primary care using depth interviews
- **Engaged Stakeholder Approach to Increase Implementation**
    - Need a Highly Engaged Stakeholder Approach to Increase Implementation
- **Primary Care: Striving for Shared Care in Survivorship**
    - Defining the provider behaviors that reflect shared care of cancer survivors (e.g., delineation and completion of tasks), specifying the processes and mechanisms that oncology specialists and primary care providers should use to facilitate shared care.

In addition to the above presentations, the NJCCR recognized the individuals below for their contribution to advancing cancer research in New Jersey.

- Senator Anthony Bucco received the Legislative Champion Award (NJ 25 District)
- Ellen Brody Decker received the Patient Advocate Award and
- Dr. Raymond Birge received the Dr. Jonathan Yavelow Mentor Award.

The Fellowship presentations were followed by a discussion on employment opportunities and trends in today's healthcare climate. The panel participants included the following:

- DR. MICHELE DONATO, HACKENSACK UNIVERSITY MEDICAL CENTER (MODERATOR)
- DR. BRITTANY ADAMSON, PRINCETON UNIVERSITY
- MARTIN REXROAD, PTC THERAPEUTICS
- ASSEMBLYMAN ANDREW ZWICKER (NJ-16)

New Jersey Commission on Cancer Research Membership

Dr. Kenneth Adler, Chair, Summit Medical Group
Dr. Kathleen Scotto, Vice-Chair, Vice-Chancellor for Research and Research Training, Rutgers Biomedical and Health Sciences,
Dr. Wendy Budin, Professor and Associate Dean for the Entry to Baccalaureate Practice at Rutgers School of Nursing,
Dr. Generosa Grana, Director of the MD Anderson Cancer Center at Cooper
Dr. Shawna Hudson, Professor and Research Division Chief in the Department of Family Medicine and Community Health, Rutgers Robert Wood Johnson Medical School
Dr. Li Li, Director, Novartis Institute for Biomedical Research
Dr. Brian Pachkowski, Division of Science and Research, New Jersey Department of Environmental Protection
Dr. Anna Marie Skalka, Professor Emerita and former W.W. Smith Chair in Cancer Research at the Institute for Cancer Research at Fox Chase Cancer Center
Loletha Johnson, New Jersey Department of Health

NJCCR Staff:
Lisa Cummings, Acting Executive Director
Jim McGarry, Consultant, Government Relations
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